Poor outcome in oocyte donation after elective transfer of a single cleavage-stage embryo in Turner syndrome patients

In this retrospective, matched study we evaluated the outcome of 31 oocyte donation (OD) cycles performed in 29 Turner syndrome (TS) patients involving the elective transfer of a single, fresh cleavage-stage (day 2 to 3) embryo. Due to the fact that ongoing pregnancy rate was statistically significantly lower (3.2% versus 22.5%) in TS patients when compared with matched, non-TS recipients, other strategies (such as single blastocyst transfer) should be evaluated that could enable better outcomes and at the same time avoid potential complications related to multiple pregnancies in this particularly high obstetric-risk group. (Fertil Steril® 2009;91:1489–92. ©2009 by American Society for Reproductive Medicine.)

Spontaneous pregnancies occur approximately in 2% to 5% of Turner syndrome (TS) patients, mainly in cases with mosaicism. However, a high risk of miscarriages and chromosomal anomalies in the offspring have been reported. Recently, the cryopreservation of ovarian tissue combined with in vitro maturation was proposed as a fertility preservation technique for a young woman with mosaic TS (1). Although this is a promising new method, the chromosome complement of retrieved oocytes is likely to be affected in a similar way to spontaneous TS pregnancies. Therefore, genetic counseling and preimplantation/prenatal diagnosis is still warranted. To date, for the majority of TS patients, oocyte donation (OD) is the only way to achieve a viable pregnancy. Pregnancy rates of TS patients after OD are thought to be similar to those of recipients with other indications. Nonetheless, to date, only a relatively small number of cases have been described (2). Many investigators reported increased rates of early pregnancy loss after OD (3–5). Obstetric outcome of achieved pregnancies is characterized by a high rate of hypertension, preeclampsia, and premature delivery (3, 6). Women with TS also have a potentially high risk of death during pregnancy from aortic rupture or dissection (7). Therefore, existing guidelines recommend thorough cardiologic screening before OD treatment as well as follow-up evaluations during pregnancy (8, 9).

To avoid additional risks related to multiple pregnancies, elective single-embryo transfer (eSET) has been recommended for this patient group (3). Although two recent reports from a Scandinavian group showed encouraging results for eSET in the setting of OD (10, 11), to date no specific reports are available on eSET in TS patients. Our retrospective analysis reports the outcome of cleavage-stage eSET in TS patients by comparing them with a matched control group of non-TS oocyte recipients.

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MATERIALS AND METHODS

After informed consent, all recipient candidates received careful assessments, including blood count, liver and renal function tests, thyroid function test, serology, and gynecologic exams with pelvic ultrasound. The uterine cavity was assessed by hysterosalpingography or hysteroscopy. To minimize cardiovascular risk during the pregnancy, a cardiologist also evaluated the TS patients, which included echocardiography and/or cardiac magnetic resonance imaging (MRI) scans. In the case of any significant alteration, the cardiologist decided whether to authorize or contraindicate fertility treatment. Oral estradiol valerate (Progynova; Schering Spain, Madrid, Spain) was used in a constant 6-mg dose regimen for endometrial preparation; and from the day of the oocyte retrieval, 800 mg of micronized vaginal progesterone (Utrogestan; Laboratorio Seid, Barcelona, Spain) was added.

A control group was created by matching every TS patient with the chronologically closest non-TS recipient who also had a single-embryo transfer with an embryo at the same stage of development (day 2 or 3) of the same quality (embryo score). The OD was anonymous and altruistic, and donors were required to be between 18 and 35 years of age. A conventional clinical and psychological workup was performed, which included karyotyping. The ovarian stimulation protocols were described previously elsewhere in detail (12). Intracytoplasmic sperm injection (ICSI) procedure was performed routinely to avoid fertilization failures. Metaphase II oocytes were injected with motile spermatozoon into the ooplasm. Developing embryos were classified according to their morphologic appearance using a modification of the combined embryo score described by Coroleu et al. (13), taking into account the number of blastomeres, their form, and the percentage of cytoplasmic

fragmentation; an optimal quality embryo scored a maximum of 10. The best available embryo was transferred into the uterine cavity using abdominal ultrasound guidance on day 2 or 3 after the ICSI procedure.

A rise in serum human chorionic gonadotropin (hCG) levels on two consecutive occasions from 14 days after transfer indicated pregnancy. In this case, hormone replacement therapy was continued until 100 days after the embryo replacement. At least one intrauterine sac revealed by ultrasonography approximately 5 weeks after transfer was considered to be a clinical pregnancy. Ongoing pregnancy was defined as a viable pregnancy confirmed on the 12th week by an ultrasound scan. Biochemical pregnancy was defined as a pregnancy loss occurring before the first ultrasound scan (6th to 7th week of pregnancy) whereas miscarriage was defined as a first-trimester loss occurring after the first ultrasound scan but before the confirmation of an ongoing pregnancy.

Institutional review board approval was not required for this study due to its retrospective nature and because study data were constantly managed in a way that excluded the identification of patients.

RESULTS

Between September 2003 and March 2008, a total of 29 patients with TS had 31 oocyte donation cycles with eSET. The chromosomal constitutions were 45X (monosomy) in 14 and mosaics or other variants in 15 patients. Five patients had had previous bilateral ovariectomy for chromosomal complement containing Y-chromosome material. All TS patients had primary amenorrhea except one patient with an Xq isochromosome. The TS patients' mean age and height was 32.8 ± 4.2 years and 151 ± 8 cm, respectively; their mean body mass index (BMI) was 24.4 ± 4.2.

One patient had preexisting, mild, treated hypertension which was well controlled, and her cardiologist had authorized pregnancy. Another 33-year-old patient had undergone surgery for aortal coarctation at 15 years of age, and her current cardiac evaluation showed no sequela related to the intervention; her cardiologist also authorized an OD attempt. Two partial uterine septa were identified in our study population, and these were corrected hysteroscopically before treatment. Another four patients had hypoplastic uteri diagnosed by hysteroscopy. Renal anomalies (horseshoe kidneys, solitary kidney, and previous unilateral nephrectomy) were identified in five patients; all had normal renal function tests. All TS patients had normal thyroid function test, including two patients who were treated for hypothyroidism.

Seven patients had undergone a total of 13 previous OD cycles (1 to 3 attempts each) in other centers. One live birth resulted from these attempts, a 2850 g infant by caesarean section after an uneventful singleton pregnancy.

Cycle data of the study and control groups are summarized in Table 1. No statistically significant differences were observed in the duration of endometrial preparation, endometrial thickness, the number of donated cumulus–oocyte complexes, or mature oocytes in the two groups. Although the number of fertilized oocytes was statistically significantly lower in the control group, it did not influence the comparison because embryo quality was the same between matched cycles. Surplus embryos were frozen for 18 and 7 patients in the TS and control group, respectively.

Seven pregnancies were obtained (22.5%) in the TS group; however, due to a high rate of early pregnancy loss (two biochemical pregnancies and four first-trimester miscarriages), the ongoing pregnancy rate was only 3.2% (1 of 31). The only ongoing pregnancy of the TS group was uneventful and ended with a birth of a healthy 3.100 g child at the 41st pregnancy week by caesarean section.

The mean recipient age in the control group was 40.5 ± 4.5 years. Ten pregnancies were obtained (32.2%), and the ongoing pregnancy rate was 22.5% (7 of 31). Four pregnancies ended with the birth of a healthy newborn, and three pregnancies are still ongoing.

TABLE 1

Cycle data of the treatment groups.

	Turner syndrome	Control group	*P* value[a]
Embryo transfers (n)	31	31	—
Duration of endometrial preparation (days)	26.6 ± 11.5	26.4 ± 10.5	.95
Endometrial thickness (mm)	10.9 ± 5	9.2 ± 1.9	.14
Donated COCs	7.2 ± 3.2	7.1 ± 2.6	.9
Donated MII oocytes	5.2 ± 1.2	5.1 ± 1.1	.75
Fertilized 2PN oocytes	3.5 ± 1.6	2.6 ± 1.4	.02
Embryo score	9.1 ± 1	9.1 ± 1.0	1.0
Frozen embryos	1.2 ± 1.4	0.4 ± 0.9	.007

Notes: Values are mean ± standard deviation. 2PN, two pronuclei; COC, cumulus–oocyte complex; MII, metaphase II.
[a] Student's *t*-test.

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Although the initial pregnancy rates were comparable between the two groups, the higher rate of early pregnancy loss made the ongoing pregnancy rate statistically significantly lower among TS patients (P=.043). Out of 18 TS patients with frozen surplus embryos, 11 patients started a frozen-thawed embryo transfer (FET) cycle. Five cycles were canceled due to nonsurvival after thawing, and seven FET cycles (with the transfer of one to two embryos) were carried out resulting in one biochemical pregnancy.

DISCUSSION

Since the advent of oocyte donation more than two decades ago (14), several reports have evaluated pregnancy rates following OD in TS patients. Published series have been of variable size, ranging from a few patients up to those reporting approximately 50 to 70 treatment cycles. Although these reports are heterogeneous, the majority of them have reported comparable pregnancy rates to those of other OD recipients with different indications. There are very few reports on obstetric outcome of OD pregnancies in TS patients (3, 6). It seems very probable, however, that these pregnancies carry a high risk of adverse obstetric outcomes such as pregnancy-induced hypertension, preeclampsia, intrauterine growth retardation, and premature delivery. These complications also occur frequently in OD pregnancies with other indications (15, 16), but because larger series of TS pregnancies are not available, intergroup comparisons are not possible. According to our own unpublished data, these complications occur frequently in singleton as well as in twin TS pregnancies.

In almost all TS pregnancies, the method of delivery is caesarean section, which may further increase the rate of postpartum complications (e.g., hemorrhage, thrombosis, infection). The increased risk of maternal death due to aortic dissection (as high as 2%) has received much attention and should not be underestimated (7). Existing guidelines recommend thorough cardiac screening before an OD attempt (8) as well as follow-up evaluations during pregnancy and the postpartum period (9).

For these reasons, eSET was strongly encouraged for the TS recipients to reduce additional risk related to multiple (twin) pregnancies. Two recent reports have shown favorable results with an eSET strategy for OD (10, 11). In the most recent of these (11), 132 embryo transfer cycles were retrospectively evaluated, and delivery rates were similarly high (30.4% vs. 30.3%) with single-embryo and double-embryo transfer, whereas the multiple rates were 0 and 40%, respectively. Although probably some TS patients were also included in that report, there are no published series available on the outcome of eSET in this particular patient group.

According to our preliminary series, eSET—at least at the cleavage-stage—does not yield favorable outcomes. Therefore, other strategies such as single-blastocyst transfer should be evaluated in the future. The recent randomized trial by Papanikolaou et al. (17) showed significantly higher delivery rates (32% vs. 21.6%) with single-blastocyst transfer when compared with cleavage-stage SET in the setting of young infertile women. The final outcome of the TS group was considerably worsened by a high rate of early pregnancy loss. A 33% to 60% pregnancy loss rate has been a constant finding in most series of TS patients who have undergone OD (2). Its cause is unknown and could be related to uterine hypoplasia/hypovascularization or some inherent endometrial receptivity defect related to the TS chromosome complement (4). Other factors such as autoimmune thyroid disease might also play a role, which has been described more frequently in TS patients. (In our study, however, patients were not systematically screened for thyroid antibodies.) Several reports have shown that uterine development is impaired in TS patients and that standard hormone replacement therapy fails to induce normal uterine development in a high proportion of patients (18, 19). A modified hormone replacement and/or hormonal regimen before OD treatment with higher doses or different routes of administration might be evaluated to overcome these negative effects; nonetheless, to date no studies have been published on this subject.

Our study has shown that in TS patients undergoing OD treatment the ongoing pregnancy rate was statistically significantly lower after eSET of a cleavage-stage embryo when compared with a matched control group of non-TS recipients. To avoid complications related to multiple pregnancies in this high-risk obstetric group, single-blastocyst transfer should be evaluated in future studies.

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REFERENCES

1. Huang JY, Tulandi T, Holzer H, Lau NM, Macdonald S, Tan SL, et al. Cryopreservation of ovarian tissue and in vitro matured oocytes in a female with mosaic Turner syndrome: case report. Hum Reprod 2008;23:336–9.
2. Delbaere A, Englert Y. Turner's syndrome and oocyte donation [in French]. Gynecol Obstet Fertil 2002;30:970–8.
3. Foudila T, Soderstrom-Anttila V, Hovatta O. Turner's syndrome and pregnancies after oocyte donation. Hum Reprod 1999;14:532–5.
4. Yaron Y, Ochshorn Y, Amit A, Yovel I, Kogosowki A, Lessing JB. Patients with Turner's syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation. Fertil Steril 1996;65:1249–52.
5. Khastgir G, Abdalla H, Thomas A, Korea L, Latarche L, Studd J. Oocyte donation in Turner's syndrome: an analysis of the factors affecting the outcome. Hum Reprod 1997;12:279–85.

6. Bodri D, Vernaeve V, Figueras F, Vidal R, Guillen JJ, Coll O. Oocyte donation in patients with Turner's syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy. Hum Reprod 2006;21:829–32.
7. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. Fertil Steril 2003;80:498–501.
8. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. Fertil Steril 2005;83:1074–5.
9. Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007;92:10–25.
10. Soderstrom-Anttila V, Vilska S, Makinen S, Foudila T, Suikkari AM. Elective single embryo transfer yields good delivery rates in oocyte donation. Hum Reprod 2003;18:1858–63.
11. Soderstrom-Anttila V, Vilska S. Five years of single embryo transfer with anonymous and non-anonymous oocyte donation. Reprod Biomed Online 2007;15:428–33.
12. Bodri D, Guillen JJ, Galindo A, Mataro D, Pujol A, Coll O. Triggering with human chorionic gonadotropin or a gonadotropin-releasing hormone agonist in gonadotropin-releasing hormone antagonist-treated oocyte donor cycles: findings of a large retrospective cohort study. Fertil Steril. Published online March 24, 2008.
13. Coroleu B, Barri PN, Carreras O, Martinez F, Parriego M, Hereter L, et al. The influence of the depth of embryo replacement into the uterine cavity on implantation rates after IVF: a controlled, ultrasound-guided study. Hum Reprod 2002;17:341–6.
14. Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. Nature 1984;307:174–5.
15. Salha O, Sharma V, Dada T, Nugent D, Rutherford AJ, Tomlinson AJ, et al. The influence of donated gametes on the incidence of hypertensive disorders of pregnancy. Hum Reprod 1999;14:2268–73.
16. Soderstrom-Anttila V. Pregnancy and child outcome after oocyte donation. Hum Reprod Update 2001;7:28–32.
17. Papanikolaou EG, Camus M, Kolibianakis EM, Van Landuyt L, Van Steirteghem A, Devroey P. In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos. N Engl J Med 2006;354:1139–46.
18. Paterson WF, Hollman AS, Donaldson MD. Poor uterine development in Turner syndrome with oral oestrogen therapy. Clin Endocrinol 2002;56:359–65.
19. Bakalov VK, Shawker T, Ceniceros I, Bondy CA. Uterine development in Turner syndrome. J Pediatr 2007;151:528–31, 31e1.